The multiple faces of artwork diagnoses

We read with interest the Focal Point by Raffaella Bianucci and colleagues[1] on the diagnosis of a short-statured woman depicted by Andrea Mantegna in the painting at La Camera degli Sposi. However, we disagree with their diagnosis of neurofibromatosis type 1 (NF1) and hypopituitary dwarfism.

Their erroneous diagnosis might have originated from the fact that the authors examined pictures of the painting dating before its restoration in the mid-1980s. In high-resolution post-restoration images, or viewed directly in loco, the signs interpreted as suggestive of NF1 are absent (figure). In particular, the spots that Bianucci and colleagues interpreted as multiple café-au-lait spots of the face are light abrasions of the pictorial surface. The lesion on the dorsal surface of the right hand that they diagnosed as a neurofibroma was probably a dirt incrustation and has disappeared in the restored version of the painting. Five facial neurofibromas are no longer visible and only three apparently sessile skin lesions remain, located between the right eye and the nose. Bianucci and colleagues also describe several Lisch nodules in both irises; however, these are easily confused with iris nevi, and their diagnosis of multiple Lisch nodules on dark irises painted on a fresco is questionable. In fact, careful observation of both the post-restoration and pre-restoration pictures does not confirm this sign. Thus, even if the three facial skin lesions were neurofibromas, the woman would not meet diagnostic criteria for NF1.

The phenotype of the woman (marked short stature with relative macrocephaly, low nasal bridge, midfacial hypoplasia, rhizomelic shortening of limbs, and small hands) allows us to make a confident diagnosis of achondroplasia. The external physical features of this condition have been known for centuries and are well represented in artwork from diverse cultures. In particular, the picture by Mantegna was reported as an example of achondroplasia in an artwork as early as 1986, and has been further reported as achondroplasia in the medical literature later on.[2,3]

***Figure*: The Court Dwarf**
Detail from La Corte (The Court) on the north wall of La Camera degli Sposi (Bridal Chamber), a room in the Castello di San Giorgio, at the Palazzo Ducale in Mantua, Italy, frescoed by Andrea Mantegna between 1465 and 1474. The artist was commissioned by the marquis of Mantua, Ludovico III Gonzaga. (A) Image captured before the restoration work of the mid-1980s. (B) Image captured after the restoration (source: photographic archive of Complesso Museale di Palazzo Ducale, Mantua, Italy). We thank Peter Assmann (Complesso Museale di Palazzo Ducale, Mantua, Italy) and the Italian Ministry of Heritage and Cultural Activities and Tourism (Complesso Museale Palazzo Ducale di Mantova, Mantua, Italy) for permission to publish the image of the restored fresco.

We declare no competing interests.

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1 Bianucci R, Perciaccante A, Appenzeller O. Painting neurofibromatosis type 1 in the 15th century. *Lancet Neurol* 2016; **15:** 1123.
2 Genetics and malformations in art. Kunze J, Nippert I. Grosse Verlag: Berlin, 1986.
3 Emery AEH, Emery M. Genetics in art. *J Med Genet* 1994; **31:** 420–22.

In their Focal Point, Raffaella Bianucci and colleagues[1] infer that the woman painted by Andrea Mantegna had neurofibromatosis type 1 (NF1) associated with hypopituitary dwarfism. However, we think that, in this portrait, the features and location of the skin nodules on the face (eg, the nasal bridge and nasolabial folds) and the right hand fit better with a diagnosis of hard fibromas of the skin, commonly seen during mature age and senescence, because on the fresco these nodules appear to be harder and more rounded than typical dermal neurofibromas.[2] It is also difficult to interpret the pigmentary changes over the cheeks and the chin as the typical café-au-lait spots of NF1. Rounded hypomelanotic macules appear over the same regions, but these macules could be regarded as intrinsic pigmentary changes of texture or attributed to the state of preservation of the fresco, rather than to the woman's skin complexion. Additionally, the large café-au-lait spots associated with NF1 very rarely (if at all) occur on the face (unlike freckling, which is frequently seen on

the perioral region).[2] The pigmentary changes nicely portrayed in both irises are unlikely to be Lisch nodules (slit-lamp examination is indispensable in the assessment of iris abnormalities);[2] if Mantegna, a universally acknowledged master of detail, painted these subtle changes in the woman's irises, we must assume that these abnormalities were evident to the naked eye, and therefore other diagnoses such as intrastromal (hyperpigmented) nevi of the iris or iris ridges (easily detected by the naked eye) rather than Lisch nodules are more likely.[2] We do not think that the deformations of fingers (ie, short bones) are a specific sign of NF1.[2] Lastly, although a larger-than-average head can be a minor feature of NF1, shorter-than-average stature, rather than dwarfism, can be also a minor feature of this phenotype.[2]

On the basis of the above considerations, we think that the woman in this painting had a skeletal dysplasia associated with dwarfism, large hands with deformed fingers, and a large head. Hence, she possibly had Kniest dysplasia or another metatropic dwarfism. Bianucci and colleagues[1] state that NF1 was first described by Ulisse Aldrovandi. Accounts of people with NF1 can be indeed traced back many years; however, the homuncio, described in the *Monstrorum Historia* by Aldrovandi,[3] is regarded as the first example of mosaic NF1, rather than NF1, and other accounts of NF1 cases existed long before Aldrovandi's description.[3–5]

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In the Focal Point "Modern diagnosis of Flaubert's death mask,"[1] the authors suggest that the French writer died of sudden unexpected death in epilepsy. However, the circumstances of his death—rising from a bathtub with blurred vision before a sudden collapse—suggest a different cause. A warm or hot bath can cause peripheral vasodilation and decrease cardiac return. Standing rapidly would also markedly decrease preload and probably trigger reflex tachycardia. This tachycardia could lead to coronary insufficiency and a ventricular arrhythmia, resulting in death.

Flaubert's clinical history of probable cardiac disease, obesity, alcoholism, and vascular syphilis would also contribute to this diagnosis.

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